REMARKS

In a restriction requirement dated November 23, 2005, the Examiner alleged that the claims were directed to three distinct inventions, and required restriction. The Examiner also required election between "polymorphisms." The Applicants elected claims directed to a method of treating hereditary lymphedema, with traverse.

On January 23, the current, new Examiner issued a second restriction requirement, alleging that the subject matter of the elected claims was, in fact, directed to five distinct inventions, and required further election. The examiner also maintained the election of polymorphisms requirement.

I. ELECTION

The Applicants hereby elect, with traverse, the claims of Group III, e.g., claims 12 and 37-51, drawn to a method of treatment for hereditary lymphedema via VEGF-C gene therapy.

The Applicants also elect polymorphism at position 1114. All of the claims of Group III are believed to be generic relative to the elected polymorphism, except claim 39.

II. TRAVERSAL

For all of the following reasons, the restriction is improper, and should be withdrawn, or the number of groups should be substantially reduced.

A. The subdivion into new Groups I-IV by restrictions relating to VEGF-C versus –D, and protein versus gens, should be withdrawn.

VEGF-C and VEGF-D share low, but detectable structural homology and share a common function as VEGFR-3 ligands. The common function is presumably attributable in part to commonalities in structure that permit both molecules to bind to the same receptor.

Proteins and genes are related insofar as the protein encodes the gene, and gene therapy involves introducing a gene to achieve in vivo expression of an encoded protein.

The MPEP (Section 803.02) instructs that, if members of a Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serous burden, the examiner *must* examine all of the members of

the Markush group on the merits, even though they may be directed to separate and distinct inventions. Section 803.04 suggests that examination of ten sequences is a reasonable number.

Because of the relatedness of the molecules recited in the Markush-style claims, the restriction .

In the alternative, the Applicants request that the protein (Groups I-II) subject matter be consolidated into one group and that the gene subject matter (Groups III and IV) be consolidated into one group. The subject matters are classified by the examiner in the same groups, and the technical differences in therapy are lesser than exists between protein and gene therapy. Accordingly, there would be little burden to examining the claims in fewer groups.

B. The election relating to polymorphisms should not be applied to claims directed to a method of treatment.

The Examiner continues to misconstrue the invention by stating, in the restriction requirement, that claim 39 "is drawn to missense mutations at multiple codons." Even if it were appropriate to restrict a claim directed to polynucleotides to specific variant forms, it would be inappropriate to apply that logic here, *because claim 39 is directed to a method of treatment.* Specifically, claim 39 depends ultimately from claim 12, directed to a method of treatment for hereditary lymphedema. Claim 39 depends more immediately from claim 37, which further defines the group of patients that is treated according to the method. Thus, the Applicants first basis for traversal is not that the polymorphisms represent indistinct inventions, but rather, that the applicants are not presently claiming the polymorphisms per se, in the elected claims.

C. Prosecution history shows that examination of method claims that are generic to multiple polymorphisms does not pose a serious burden.

The Examiner's search will entail a search for prior art relating to treatment of hereditary lymphedema in a generic sense. In the course of examining the generic claims,

there will be no serious burden in considering claims that recite any of the five mutations identified in the restriction.[1]

To the extent that there is a search burden relating to identifying patient populations that will benefit from the treatment due to polymorphisms, the prosecution history of the parent application already establishes that no serious burden exists. The first six issued claims of parent U.S. Patent No. 6,764,820, reproduced below, relate to assaying for risk of developing heritable lymphedema. Claim 1 is generic to *any* alteration that reduces VEGFR-3 signalling. Claim 2-3 are subgeneric to mutations that alter tyrosine kinase domain amino acids. Claims 4-6 recite either a markush group of polymorphisms, or a single polymorphism:

> 1. A method of assaying for risk of developing hereditary lymphedema, comprising assaying nucleic acid of a human subject for a mutation that alters the encoded amino avid sequence of at least one VEGFR-3 allele of the human subject and reduces ligand-mediated signaling of the VEGFR-3 polypeptide encoded by the allele, when compared to VEGFR-3 encoded by a wild-type human VEGFR-3 allele;
>
> wherein presence of said mutation in the nucleic acid correlates with an increased risk of developing hereditary lymphedema, and wherein absence of said mutation in the nucleic acid correlates with no increased risk of developing hereditary lymphedema.
>
> 2. A method according to claim 1 wherein the assaying step comprises assaying for a mutation altering a tyrosine kinase domain amino acid sequence of the protein encoded by the VEGFR-3 allele.
>
> 3. A method according to claim 2 wherein the assaying identifies a mutation altering a tyrosine kinase domain amino acid sequence of the protein encoded by the VEGFR-3 allele.
>
> 4. A method according to claim 1 wherein the assaying step comprises assaying for a missense mutation in a VEGFR-3 allele at a position corresponding to one of codons 857, 1041, 1044 and 1049 of the VEGFR-3-encoding sequence set forth in SEQ ID NO: 1.
>
> 5. A method according to claim 4 wherein the assaying identifies the missense mutation in a VEGFR-3 allele in the human

[1] Even in circumstances where election of species is appropriate, the rules contemplate an examiner permitting a reasonable number of species.

subject.

6. A method according to claim 1 wherein the assaying step comprises assaying for a missense mutation in a VEGFR-3 allele at a position corresponding to codon 1114 of the VEGFR-3-encoding sequence set forth in SEQ ID NO:1.

Thus, the first examiner that looked at this application has already determined that a different set of method claims could be examined, without limitation to a single polymorphism, without serious burden. Importantly, the generic claims were already determined to be allowable by the first examiner.

Using prosecution of the parent application as a guide, the restriction relating to polymorphism species should be withdrawn, because it serves no useful purpose.

D. The election relating to polymorphisms should be withdrawn upon allowance of a generic claim.

The applicants acknowledge with thanks the re-casting of the polymorphism issue as an election of species issue. Even if maintained for now, it should be withdrawn if/when generic claims are shown to be allowable.

III. Conclusion

In view of the foregoing, the Applicants request withdrawal of the restriction requirement and allowance of all claims.

Dated: Marchr 23, 2006

Respectfully submitted,

By: 

David A. Gass
Registration No.: 38,153
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorneys for Applicants